alphaB-Crystallin Regulates Subretinal Fibrosis by Modulation of Epithelial-Mesenchymal Transition.

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Public Summary:
This study demonstrates, for the first time, the functional role of αB-crystallin in epithelial-mesenchymal transition (EMT) of retinal pigment epithelium (RPE) cells and its association with subretinal fibrosis.

Scientific Abstract:
Subretinal fibrosis is an end stage of neovascular age-related macular degeneration, characterized by fibrous membrane formation after choroidal neovascularization. An initial step of the pathogenesis is an epithelial-mesenchymal transition (EMT) of retinal pigment epithelium cells. alphaB-crystallin plays multiple roles in age-related macular degeneration, including cytoprotection and angiogenesis. However, the role of alphaB-crystallin in subretinal EMT and fibrosis is unknown. Herein, we showed attenuation of subretinal fibrosis after regression of laser-induced choroidal neovascularization and a decrease in mesenchymal retinal pigment epithelium cells in alphaB-crystallin knockout mice compared with wild-type mice. alphaB-crystallin was prominently expressed in subretinal fibrotic lesions in mice. In vitro, overexpression of alphaB-crystallin induced EMT, whereas suppression of alphaB-crystallin induced a mesenchymal-epithelial transition. Transforming growth factor-beta2-induced EMT was further enhanced by overexpression of alphaB-crystallin but was inhibited by suppression of alphaB-crystallin. Silencing of alphaB-crystallin inhibited multiple fibrotic processes, including cell proliferation, migration, and fibronectin production. Bone morphogenetic protein 4 up-regulated alphaB-crystallin, and its EMT induction was inhibited by knockdown of alphaB-crystallin. Furthermore, inhibition of alphaB-crystallin enhanced monotetraubiquitination of SMAD4, which can impair its nuclear localization. Overexpression of alphaB-crystallin enhanced nuclear translocation and accumulation of SMAD4 and SMAD5. Thus, alphaB-crystallin is an important regulator of EMT, acting as a molecular chaperone for SMAD4 and as its potential therapeutic target for preventing subretinal fibrosis development in neovascular age-related macular degeneration.